Boehringer Ingelheim

Clinical Trial Protocol

	Document Number: **c36797272-01**
BI Trial No.	1297-0015
BI Investigational Medicinal Product(s)	BI 695501 40 mg/0.4 mL; 100 mg/mL (T) BI 695501 40 mg/0.8 mL; 50 mg/mL (R)
Title	Relative bioavailability of 40 mg/0.4 mL of BI 695501 compared to 40 mg/0.8 mL of BI 695501 formulation following single subcutaneous administration in healthy male and female subjects (a double blind, randomized, single-dose, parallel-arm study).
Lay Title	A study in healthy people to test how 2 different formulations of BI 695501 are taken up by the body when given as an injection
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
Coordinating Investigator	[redacted]
Current Version, Date	Version 1.0, 26 November 2021
Original Protocol Date	26 Nov 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	26 November 2021
Revision date	Not applicable
BI trial number	1297-0015
Title of trial	Relative bioavailability of 40 mg/0.4 mL of BI 695501 compared to 40 mg/0.8 mL of BI 695501 formulation following single subcutaneous administration in healthy male and female subjects (a double blind, randomised, single-dose, parallel-arm study).
Coordinating Investigator	[redacted]
Trial site(s)	Multicenter trial to be conducted in two sites: [redacted]
Clinical phase	I
Trial rationale	Relative bioavailability of a test product (40 mg BI 695501 100 mg/ml, 0.4 ml) compared to the reference product (40 mg BI 695501 50 mg/ml, 0.8 ml) is to be investigated
Trial objective	The main objective of this trial is to compare the pharmacokinetics (PK) of 40 mg BI 695501 100 mg/mL with 40 mg BI 695501 50 mg/mL following single subcutaneous administration.
Trial endpoints	Primary endpoints: $AUC_{0-\infty}$, AUC_{0-1344} and C_{max} of BI 695501 Secondary endpoints: No secondary endpoints defined
Trial design	Double blind, randomised, single-dose, parallel-arm study
Number of subjects **total entered** **on each treatment**	 200 100
Diagnosis	Not applicable
Main inclusion criteria	Healthy male/female subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m2 (inclusive)
Test product	BI 695501 Solution for injection in prefilled syringe (T)

dose	40 mg / 0.4 mL / 100 mg/mL
mode of administration	Subcutaneous injection
Reference product	BI 695501 Solution for injection in prefilled syringe (R)
dose	40 mg / 0.8 mL / 50 mg/mL
mode of admin.	Subcutaneous injection
Duration of treatment	Single dose administration trial followed by a 57-day observation period and up to 70 days safety follow up period
Statistical methods	Relative bioavailability of 40 mg/ 0.4 ml BI 695501 formulation (Test, T) compared to 40 mg/ 0.8 ml of BI 695501 formulation (Reference, R) will be estimated by the ratios of the geometric means (T/R) for the primary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of covariance (ANCOVA) on the logarithmic scale including effects for 'treatment', 'location of trial medication injection' and 'baseline body weight'. CIs will be calculated based on the residual error from the ANCOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time [h:min]	Approx. time (actual time) [h:min][6]	Event and comment	Laboratory/ Urinalysis[4]	Injection site / Local tolerability Assessment	PK_{blood}	[redacted]	[redacted]	Physical Exam	12-lead ECG	Vital signs (BP, PR and Temp[3])	AE/Concomitant Mediation
1	-28 to -2			Screening	A[7]					X	X	X	▲▼
	-1			Admission to trial center	B[7,8]					X	X	X	X
	1	-1:00	7:00	Predose		X	X	X	X				X
		0:00	8:00	Drug administration									
		0:30	8:30			X							X
		4:00	12:00			X	X					X	X
		12:00	20:00				X						X
	2	24:00	8:00	Discharge from trial site		X	X			X	X	X	X
	3	48:00	8:00	Ambulatory visit			X						X
	4	72:00	8:00	Ambulatory visit			X						▲
	5	96:00	8:00	Ambulatory visit			X						|
	6	120:00	8:00	Ambulatory visit			X						|
	7	144:00	8:00	Ambulatory visit			X						|
	8	168:00	8:00	Ambulatory visit			X						|
	10	216:00	8:00	Ambulatory visit	B		X			X	X	X	|
	15	336:00	8:00	Ambulatory visit			X	X	X				|
	22	504:00	8:00	Ambulatory visit	B		X			X	X	X	|
	29	672:00	8:00	Ambulatory visit			X	X	X				|
	36	840:00	8:00	Ambulatory visit			X						|
	43	1008	8:00	Ambulatory visit			X						|
3	57	1344	8:00	Ambulatory e.o.t.	D[8]		X	X	X	X	X	X	▼
	70			Safety Follow-up (e.o.s.)[5]									X

Note: Please refer to table 1 for specific planned time points.

1. Days -1 to 2 will be inpatient visits. Days 3 to 57 (e.o.t.) will be outpatient/ambulatory visits.
2. Subjects who discontinue the trial early will have all assessments completed as identified for the e.o.t visit.
3. Temperature may be measured orally or aurally; however, should be consistent for all assessments at a given trial site.
4. Full laboratory testing inclusive IGRA-T will be performed at screening and e.o.t.; Abbreviated laboratory testing will be performed on Day -1, 10, 22, 57 according to the Table 5.2.3:1, and at the investigator's discretion.
5. Day 70 (e.o.s.): subjects will be contacted to collect safety data.
6. Flowchart represents an example based on a drug administration time of 8:00 in the morning. If the drug administration time is shifted, all other measurements specified in the flowchart have to be shifted accordingly.
7. SARS-CoV-2 PCR test will be performed at screening shortly (within 72 hours) before admission to the site
8. Including Urine β-hCG

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ABBREVIATIONS AND DEFINITIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	anti-hepatitis B core antibodies
anti-HCV	hepatitis C antibodies
AST	aspartate aminotransferase
AUC	area under the curve
β-hCG	beta-human chorionic gonadotropin
BI	Boehringer Ingelheim
BLQ	below the limit of quantitation
BSA	body surface area
CA	competent authority
CI	confidence interval
Cmax	maximum concentration of the analyte in plasma
Cmin	minimum concentration of the analyte in plasma
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	coefficient of variation
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
DRM	Data Review Meeting
ECG	electrocardiogram
eCRF	electronic Case Report Form
EoT	End-of-Treatment
EU	European Union

EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon gamma-release assay
IL	interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	intrauterine device
i.v.	intravenous
K2EDTA	dipotassium ethylenediaminetetraacetic acid
LPDD	Last Patient Drug Discontinuation
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MTX	methotrexate
[redacted]	[redacted]
NOA	not analysed
NOR	no valide result
NOS	no sample
NRI	non-responder imputation
NSAID	non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PASI50	50% reduction in Psoriasis Area and Severity Index

PASI75	75% reduction in Psoriasis Area and Severity Index
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Set
PPD	purified protein derivative
PPS	Per-Protocol Set
PUVA	psoralen with ultraviolet light
RA	rheumatoid arthritis
REP	residual effect period
RTS	Run-in Treated Set
SAE	serious adverse event
s.c.	subcutaneous
SFU	Safety Follow-up
SOP	standard operating procedure
SPC	summary of product characteristics
sPGA	Static Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
tmax	time to reach maximum concentration
tmin	time to reach minimum concentration
TNF	Tumor necrosis factor
TNFR1	tumor necrosis factor 1
TNFR2	tumor necrosis factor 2
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	upper limit of normal
US	United States
US-PI	United States Prescribing Information
WHO	World Health Organisation
ADME	Absorption, distribution, metabolism, and excretion

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The biologic tumor necrosis factor (TNF) antagonists, including the human monoclonal antibody (mAb) adalimumab (Humira®, Abbott), are generally preferred as first-line biologic therapy. Tumor necrosis factor is a naturally occurring cytokine that is involved in normal inflammatory and immune responses.
Humira® (adalimumab) was first launched in 2002 for the treatment of active moderately to severely active rheumatoid arthritis. As of February 2019, Humira® is approved for many indications (R18-2637, R19-0075) in the US and EU

1.2 DRUG PROFILE

BI 695501 is a monoclonal antibody, developed and approved as a biosimilar to the TNF-alpha blocker Humira® under the trade name Cyltezo®. The marketing authorisation application and aBLA seeking registration of Cyltezo® as a biosimilar to Humira® (adalimumab) were submitted to US FDA in October 2016, and the FDA approved it on 25 Aug 2017 (R17-4157).
Adalimumab is a recombinant human monoclonal immunoglobulin (Ig) GI antibody specific to human TNF-alpha. Humira binds specifically to TNF-alpha (and not TNF-beta) and blocks its interaction with the TNF receptors, TNFR1 and TNFR2. It has human derived heavy and light chain variable regions and human IgG1:k constant regions and is produced in a mammalian expression system (R18-2637, R19-0075).

The preclinical studies that support the clinical program included:

- A comparative 5-week toxicology trial with an 8-week recovery in cynomolgus monkeys comparing BI 695501 and Humira. There was no difference in systemic exposure between BI 695501 and Humira with repeated dosing. This trial demonstrated the similarity of the toxicology profile for BI 695501 and Humira.
- A single dose pharmacokinetic (PK), subcutaneous (s.c.) trial in cynomolgus monkeys comparing BI 695501 to Humira. There were no differences in the exposure or antidrug antibody (ADA) response in cynomolgus monkeys to BI 695501 and Humira.
- A comparative human tissue cross-reactivity trial of BI 695501 and Humira. This trial showed that the patterns of staining of BI 695501 and Humira were similar with minor differences attributable to section to section variation, rather than any true staining differences. All of the tissue cross-reactivity staining was consistent with reported sites of TNF expression and/or previously reported sites of reference product cross-reactivity.
- A determination of the potential other cytokines to bind to BI 695501 or inhibit binding of BI 695501 to TNF compared to Humira. None of the three antibodies bound to any of the 8 other cytokines that were tested. Additionally, there was no difference in the effect of these cytokines on the binding of TNF between BI 695501 and Humira.

- The potential for BI 695501 to induce *in vitro* cytokine release or directly activate complement compared to Humira. The results from this trial demonstrated that BI 695501 and Humira are not anticipated to induce cytokine release in humans and do not directly activate complement.
- An irritation potential trial in rabbits with BI 695501 demonstrated that BI 695501 did not cause irritation.

Clinical studies

A total of 408 healthy subjects have been treated with BI 695501 in 4 phase I studies investigating single administrations of BI 695501 (408) or Humira (342) (U13-1096-01, c03070713, c08933656, c15874906). There were no notable differences between BI 695501 and Humira and between PFS and AI with respect to safety, tolerability, and immunogenicity. Overall, the adverse events (AEs) seen in healthy subject trials were in line with the known safety profile of Humira (R18-2637, R19-0075).

A total of 1060 patients have been treated with BI 695501 including patients with RA, Crohn´s disease and plaque psoriasis.
Overall, the safety profile of BI 695501 observed in the clinical trials is considered similar to and consistent with the known safety profile of Humira®. The trials showed that BI 695501 and Humira are highly similar in terms of efficacy over a treatment duration up to 48 weeks. The results of the immunogenicity assessment across trials demonstrated a comparable immunogenicity profiles.
Cyltezo® is approved for the following indications in the US:

- Rheumatoid arthritis
- Juvenile idiopathic arthritis
- Axial spondyloarthritis
- Psoriatic arthritis
- Crohn’s disease
- Paediatric Crohn's disease
- Psoriasis
- Paediatric plaque psoriasis
- Ulcerative colitis
- Uveitis

For a more detailed description of the BI 695501 (Cyltezo®) profile, please refer to the current Investigator’s Brochure (IB) [c01835608]

1.2.1 Residual Effect Period

The Residual Effect Period (REP) of BI 695501 is 70 days. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 695501 is being developed in two different formulations, 50 mg/mL per 0.8 mL solution for injection (current formulation) and 100 mg/mL per 0.4 mL solution for injection (HCLF), both containing the same amount of the drug product - 40 mg BI 695501. Pursuant to the Guidance for industry, the relative bioavailability of a test product (40 mg BI 695501, 100 mg/ml, 0.4 ml) compared to the reference product (40 mg BI 695501, 50 mg/ml, 0.8 ml) is to be investigated.
Additionally, clinical data to support the safety, including [redacted] and local tolerability will be evaluated.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this trial is without any (therapeutic) benefit for healthy subjects. Their participation in the trial, however, is of major importance to the development of the BI 695501 lower volume formulation to be used for patient's treatment. The subjects are exposed to the risks of the trial procedures and the risks related to the exposure to the trial medication.

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venepuncture for blood sampling.
The total volume of blood withdrawn during the entire trial per subject will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from this blood withdrawal.
The needle cap on the prefilled syringe contains dry natural rubber. In rare cases this may cause severe allergic reactions. However, since the injection will be performed by the experienced medical personnel, the risks will be minimized. Subjects with a known history of allergic reactions will not be included into the trial.

Drug-related risks and safety measures

Adalimumab (BI 695501 (Cyltezo®), Humira) has a generally favorable clinical safety profile, and is not associated with AEs that would suggest a high risk to subjects participating in this trial. In patients treated with Humira, most common adverse reactions (incidence >10%) include infections (e.g. upper respiratory, sinusitis), injection site reactions, headache

and rash, abdominal pain, musculoskeletal pain, nausea and vomiting. Allergic reactions (e.g. allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

Cases of hepatitis B virus (HBV) reactivation have been reported in patients receiving anti TNF therapy. Some cases have been fatal, the majority of which were in patients concomitantly receiving other immunosuppressive medications.

Tuberculosis (TB) reactivation or new TB infections have been observed in patients receiving Humira and other TNF-inhibitors, including patients who had previously received treatment for latent or active TB.
To avoid a risk of reactivating TB and other infections, TB tests (interferon-gamma release assay [IGRA]), Hepatitis B Surface Antigen (qualitative), Hepatitis B Antibody (qualitative), Hepatitis C Antibodies (qualitative), human immunodeficiency virus (HIV)-1 and HIV-2 Antibody (qualitative) will be performed prior to dosing to exclude subjects tested positive. Risk to subjects will also be minimized in this trial by implementing conservative eligibility criteria.

In the controlled portions of clinical trials of some TNF-inhibitors, including Humira, more cases of malignancies have been observed among TNF-inhibitor-treated adult patients compared to control-treated adult patients when treated with multiple doses. However, the possible risk for the development of malignancies cannot be excluded.

Further information regarding relevant contraindications, special precautions, adverse reactions and other recommendations for the use of US-licensed Humira and EU-approved Humira are described in the prescribing information (R18-2637, R19-0075).

The PK similarity of BI 695501 to US-licensed and EU-approved Humira was established (c03070713). Additionally, there were no notable differences with respect to safety, tolerability and immunogenicity between groups and the dose of 40 mg BI 695501 was safe and well tolerated in young healthy volunteers. The AE with the highest incidence in the 108 subjects who received BI 695501 in trial 1297.8 was headache (25 subjects, 23.1%), followed by upper respiratory tract infections (19 subjects, 17.6%). However, there was no difference in the AE profile between BI 695501 to US licensed and EU-approved Humira®. There were no clinically relevant findings with respect to clinical laboratory evaluation, vital signs, electrocardiograms (ECGs), or injection site reactions.

The subjects will be kept in a Phase I unit for 24 hours after trial medication administration for safety evaluations and blood samples draws. A careful clinical examination will be performed before the subjects are discharged from the clinic, during the trial and at the end of trial visit.

Subjects will be followed up during outpatient ambulatory visits. The ambulatory visits will occur on Days 1-8, 10, 15, 22, 29, 36, 43 and 57 (End-of-Treatment [e.o.t.]) and will allow for collection of safety signs and symptoms that may occur or arise following trial treatment. Adverse events, body temperature, vital signs, ECGs and safety laboratories as well as

[redacted] will be monitored at different time points during the trial. During the long term safety follow-up period all AEs, regardless of relatedness, will be collected until 10 weeks after the administration of trial medication.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety.
In addition, hypersensitivity reactions, anaphylaxis, and serious infections are considered as adverse events of special interest (AESI), see Section 5.2.6.1.4.

Based upon preclinical and clinical information available to date, healthy subjects in this trial will not be exposed to undue safety risks.

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 695501 is well understood.

In the context of the unmet medical need and anticipated benefit of BI 695501, the benefit risk evaluation of the compound, based upon the available preclinical and clinical information, is favourable.

Considering the medical need for the development of a better tolerated and more effective treatment for patients with BI 695501, the expected benefit outweighs the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the relative bioavailability of 40 mg BI 695501 100 mg/mL (test) versus 40 mg BI 695501 50 mg/mL (reference) following single subcutaneous administration.

2.1.2 Primary endpoint(s)

The following pharmacokinetic parameters will be determined for 40 mg BI 695501 100 mg/mL and 40 mg BI 695501 50 mg/mL:

- AUC_{0-1344} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 1344 hours after dose administration)

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

Not applicable.

[redacted]

[redacted]

2.2.2.2 Safety and tolerability

Safety and tolerability of 40 mg BI 695501 100 mg/mL and 40 mg BI 695501 50 mg/mL will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination or 12-lead ECG)
- Safety laboratory tests
- Local tolerability
- Vital signs (BP, PR)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a randomized, single-dose, double blind, parallel arm trial in healthy male and female subjects aged ≥18 to ≤55 years.
It is planned to include 200 healthy male and female subjects into the trial to ensure at least 190 subjects for the primary analysis. Subjects will be randomly assigned to receive one dose of either BI 695501 40 mg/0.4 mL (T) or BI 695501 40 mg/0.8 mL (R). All study drugs will be administered by subcutaneous injection.

The trial will consist of a Screening period of up to a maximum of 28 days. The subject will check-in to the trial center on Day -1, will be dosed on Day 1. All subjects will remain in the clinic until day 2 after dosing. The subject will then return to the clinic for 13 ambulatory visits on Days 3, 4, 5, 6, 7, 8, 10, 15, 22, 29, 36, 43 and 57 (e.o.t.).

Additionally, all AEs, regardless of relatedness, will be collected until 10 weeks after the administration of trial medication. Adverse events not fully resolved at the Safety Follow-up visit will be followed until recovery or in case of persistency, sufficient characterization has been achieved and the investigator and medical monitor agree to not pursue them further.
An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

This is a 14-week, double blind, randomized, single dose, parallel arm trial to investigate and compare the PK, safety, tolerability and immunogenicity of two formulations of BI 695501 administered subcutaneously via prefilled syringe.

Due to the long half-life of BI 695501, a parallel group design was selected, with administration of BI 695501 as a single dose only. Additionally, randomization minimizes selection bias between the treatment groups.

The trial endpoints are derived from measurement of plasma concentrations of the analyte provided by a bioanalytical laboratory which is blinded to treatment allocation.

The group size of up to 100 subjects per treatment group is considered adequate for an evaluation of the PK, safety, tolerability, [redacted].

3.3 SELECTION OF TRIAL POPULATION

It is planned that 200 healthy male and female subjects will enter the trial. They will be recruited from the volunteers' pool of the trial sites.

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF, irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

Subjects will only be included in the trial if they meet the following criteria:

1. Healthy male or female subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs, 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
5. Participants of reproductive potential (childbearing potential[1]) must be willing and able to use highly effective methods of birth control per International Council for Harmonisation (ICH) M3 (R2) that result in a low failure rate of less than 1% per year from at least 30 days before administration of the trial medication until 30 days after trial completion. A list of contraception methods meeting these criteria is provided in the Section 4.2.2.3 and ICF.

3.3.3 Exclusion criteria

Subjects will not be allowed to participate, if any of the following general criteria apply:

1. Previous exposure to adalimumab or proposed adalimumab biosimilar drugs.
2. Any finding in the medical examination (including BP, PR or ECG) that deviates from normal and judged as clinically relevant by the investigator.
3. Any evidence of a concomitant disease judged as clinically relevant by the investigator including gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, hormonal disorders or diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders.
4. History of relevant orthostatic hypotension, fainting spells, or blackouts.
5. Chronic or relevant acute infections.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

6. Positive result for HIV, HBV, and hepatitis C (Hep C) at screening.
7. History of relevant allergy or hypersensitivity including allergy to the trial medication, its excipients or device materials (e.g. natural rubber or latex).
8. Within 10 days prior to administration of trial medication, use of drugs that might reasonably influence the results of the trial.
9. Intake of an investigational drug in another trial within 30 days or 5 half-lives (whichever longer) prior to planned administration of the trial medication in this trial or intake of an investigational drug during the course of this trial.
10. Alcohol abuse (consumption of more than 28 units/week).
11. Unwillingness/inability to refrain from intake of alcoholic beverages from 48 hours prior to the trial medication administration and until Day 14 post trial medication administration; and/or to limit alcohol intake to a maximum of 3 units per day until e.o.t.
12. Drug abuse or positive drug screening.
13. Blood donation of more than 500 mL within 30 days prior to administration of trial medication or intended donation during the trial.
14. Intention to perform excessive physical activities within 4 days prior to administration of trial medication or contact sport during the entire trial and unwilling to avoid vigorous exercise for 14 days post dosing.
15. Inability to comply with dietary regimen of trial site.
16. Any out-of-range laboratory values considered clinically significant by the investigator; (subjects with creatine kinase (CK) values 2 times the upper limit of normal (ULN) at Day -1 are to be) excluded from participation).
17. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because [redacted] is considered not able to understand and comply with trial requirements, or has a condition that would not allow safe participation in the trial.
18. Subjects with any immunological disorders or auto-immune disorders, (e.g., RA, lupus erythematosus, scleroderma, etc.).
19. Subject has received a live vaccine within 12 weeks prior to enrolling in the trial, or planned to be vaccinated with any vaccine during the study
20. History of TB or positive finding in IGRA.
21. Evidence of skin irritation or infection at the planned injection place.
22. Currently enrolled in another investigational device or drug study
23. Any condition that, in the investigator's opinion, makes them an unreliable study subject or unlikely to complete the trial
24. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
25. During COVID-19 pandemic*: laboratory test indicative of an ongoing SARS-CoV-2 infection

*Participants enrolled to the study should be either fully vaccinated or recovered at least 2 weeks prior to the study start.

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.1, the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events (AEs), or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

If new efficacy or safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for any of the following reasons (if reasons 4 and/or 5 are met, the trial should be discontinued immediately):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

3.3.5 Replacement of subjects

In case more than 10 subjects do not complete the trial (including subjects non- evaluable for PK), additional subjects may be recruited and treated with the respective treatment if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced and no additional subject will be recruited in such a case. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced, i.e. recruited in addition. The total number of replacements may not exceed 1/4 of the total number of evaluable subjects anticipated to complete the trial. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Test product:

Substance:	BI 695501
Pharmaceutical formulation:	Solution for injection in prefilled syringe
Source:	Boehringer Ingelheim
Unit strength:	40 mg / 0.4 mL / 100 mg/mL
Posology:	1-0-0*
Route of administration:	s.c.
Duration of use:	single dose

Reference product:

Substance:	BI 695501
Pharmaceutical formulation:	Solution for injection in prefilled syringe
Source:	Boehringer Ingelheim
Unit strength:	40 mg / 0.8 mL / 50 mg/mL
Posology:	1-0-0*
Route of administration:	s.c.
Duration of use:	single dose

*administered in the morning

BI 695501 will be provided as sterile, preservative-free, non-pyrogenic, single-use prefilled glass syringes containing 40 mg of BI 695501 per 0.4 or 0.8 mL. One syringe will be used per injection. The needle cap of the syringe contains dry, natural rubber.

4.1.2 Selection of doses in the trial

The dose selected for this trial reflects the standard clinical dose, and established similarity to the originator compound. The design and handling of the BI 695501 prefilled syringes are standard, and intended to be marketed.

4.1.3 Method of assigning subjects to treatment groups

The randomisation scheme will be provided to the trial sites in advance.

Once a subject number has been assigned, it cannot be reassigned to any other subject.

Several subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required.

The randomisation procedure is described in Section 7.4.

4.1.4 Drug assignment and administration of doses for each subject

This is a single dose trial. All subjects will receive one of two possible treatments in a randomized order. The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	BI 695501	Solution for injection in PFS	100 mg/mL	0.4 mL	40 mg
R (Reference)	BI 695501	Solution for injection in PFS	50 mg/mL	0.8 mL	40 mg

The prefilled syringes should be taken out of the fridge and wait approximately 30 minutes before administration, to permit the medication to warm to room temperature. Injecting cold medication can cause discomfort. Once taken out of the refrigerator, the trial medication should be administered within approx. 1 hour. A syringe must not be used if it is frozen or if it has been left in direct sunlight.

Trial medication will be administered as a single, s.c. injection while the subject is in a supine position by the trained investigator or designee. The time, injection location, and any difficulties with injection of the trial medication administration will be recorded in the eCRF. The location for the trial medication injection will be the lower abdomen (excluding a 2-inch [5-cm] area around the navel) or upper thigh. Each injection site should be used for at least 60 subjects (~30%), preferably 100 subjects (i.e. 50%) of the study population. Detailed "Instructions for use" are provided in the Appendix 10.1 and will be provided in the ISF. Subjects will be kept under close medical surveillance until 24 hours following trial medication administration.

Standardized meals will be served during the residential period.

4.1.5 Blinding and procedures for unblinding

This is a double-blind trial, therefore patients, investigators, and everyone involved in clinical conduct (except the trial personnel administering the trial medication – third party blinding) will remain blinded with regard to the randomized treatment assignments until after database lock.

The unblinded site personnel administering the trial medication will not be involved in any other trial assessments or procedures.

Details of blinding procedures are described in Appendix 10.2 Medication Blinding Procedures.

The secondary packaging (boxes containing PFS) will be identical for both BI 695501 40 mg per 0.4 or 0.8 mL, allowing the blinding of the site pharmacy.

The data will be unblinded at the time point of the primary analysis (see Section 7.4), only for individuals involved in the primary analysis and reporting.

Access to the randomization code will be controlled and documented. All persons directly involved in the conduct of the trial will have no access to the treatment allocation prior to final database lock.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

Emergency envelopes will not be provided, since all subjects will receive the same dose of the same drug.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

For details of packing and the description of the label, refer to the ISF.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the

Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol
- Availability of FDA Form 1572

Only authorised personnel documented in the form 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed except for hormonal contraceptives or ovary hormone replacement; limited amounts of paracetamol (or ibuprofen) are allowed to treat aches and pains. Supplements and herbal preparations are discouraged from use during the course of the trial. Vitamins may be used during the trial based on the discretion of the investigator.

Any live or attenuated vaccines are strictly prohibited during the course of the trial.
Use of any prescribed or over-the counter drugs should be reported and discussed with the investigator.

The subjects are instructed not to undergo any medical treatment or any surgical procedure 14 days prior to, during and until the end of the trial without having informed the investigator or [redacted] deputy unless necessary to treat medical emergencies.

All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff and are restricted from smoking. Standardised meals will be served at the standard times.

On all days when safety laboratory sampling is planned, subjects must have fasted for at least 6 hours prior to blood samples being collected.

Excessive exercise should be avoided from 4 days prior to and up to 14 days after trial medication administration. Contact sport must be avoided for the duration of the trial.

Subjects should abstain from alcoholic beverages for 24 hours prior to each trial visit. Alcoholic beverages are not permitted from 48 hours prior to the first trial medication administration on Day 1 and until Day 14 and then no more than three units of alcohol per day are allowed until e.o.t.
One unit of alcohol is 10 mL (1 cL) by volume, or 8 g by weight, of pure alcohol. For example:
One unit of alcohol is about equal to:

- Half a pint (290 mL) of ordinary strength beer, lager, or cider (3% to 4% alcohol by volume); or
- A small pub measure (25 mL) of spirits (40% alcohol by volume): or
- A standard pub measure (50 mL) of fortified wine such as sherry or port (20% alcohol by volume).

There are one and a half units of alcohol in:

- A small glass (125 mL) of ordinary strength wine (12% alcohol by volume); or

- A standard pub measure (35 mL) of spirits (40% alcohol by volume).

4.2.2.3 Contraception requirements

A serum beta-human Chorionic Gonadotropin (β-hCG) test will be performed at Screening in women of childbearing potential. A local urine pregnancy test will be then performed as indicated in the Flow Chart. Any woman with a confirmed positive pregnancy test during screening is not eligible for the trial. A positive urine pregnancy test during the study duration should be reported and followed up.
Female subjects and Male subjects with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception from at least 30 days before the first administration of trial medication, during the trial and until 30 days after trial completion. Males and male partners of female subjects should use a condom.

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial. Acceptable methods of birth control include, for example: combined (estrogen and progestogen containing) hormonal contraception that prevents ovulation (oral, intravaginal or transdermal); progestogen-only hormonal contraception that inhibits ovulation (only injectables or implants); intrauterine devices (IUDs) or intrauterine hormone-releasing system (IUS); surgical sterilization; vasectomized partner or be Sexually abstinent.

Women of childbearing potential are defined as:

- Having experienced menarche and
- Not postmenopausal (12 months with no menses without an alternative medical cause) and
- Not permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

Women must not breast-feed for at least six months after the adalimumab treatment.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations of trial medication will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, BMI, smoking and alcohol history (smoking/alcohol history not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, T), 12-lead ECG, laboratory tests, and a physical examination. The physical examination will include assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular and neurological systems, thyroid gland, musculoskeletal system/limbs, respiratory tract and abdomen. Clinically relevant abnormal findings will be reported as baseline conditions or AEs.
At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (e.g. Welch Allyn Spot Vital Signs LXi) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible. Body temperature (T) will also be recorded. The method of measuring body temperature (oral/aural) should be consistent at a specific trial site.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 6 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

The parameters to be assessed are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	D
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)				
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Creatine Kinase [CK]	X	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--

Table 5.2.3: 1 Routine laboratory tests (cont.)

Substrates	Glucose (Plasma) Creatinine Bilirubin, Total Bilirubin, Direct (if total elevated) Albumin (Protein Electrophoresis) Alpha-1-Globulin (Protein Electrophoresis) Alpha-2-Globulin (Protein Electrophoresis) Beta-Globulin (Protein Electrophoresis) Gamma-Globulin (Protein Electrophoresis) C-Reactive Protein (Quant) Uric Acid	X X X X X X X X X X X X	 X X X	 X X X
Serum Pregnancy test (only for female subjects of childbearing potential) at screening and if urine pregnancy test is positive	Human Serum Chorionic Gonadotropin	X		
Electrolytes	Sodium Potassium	X X		
Urinalysis (Stix)	Urine Nitrite (qual) Urine Protein (qual) Urine Ketone (qual) Urine RBC/Erythrocytes (qual) Urine WBC/Leucocytes (qual) Urine pH	X X X X X X		
Urine Pregnancy test (only for female subjects of childbearing potential) at randomization as indicated in the Flow Chart (including EoT)	Human Chorionic Gonadotropin in the urine		X	

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Day -1, 10, 22 (for time points refer to Flow Chart)
D: parameters to be determined at Visit 3 (end of trial examination)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy tests and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to randomisation, and as part of the end of trial examination. Drug screening will be performed at screening and prior to randomisation.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine Benzodiazepine Cannabis Cocaine Methadone Methamphetamines Opiates Phencyclidine
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
Tuberculosis	IGRA-T (e.g. QuantiFERON®-TB Gold IT Test)
COVID 19 infection	SARS-CoV-2 virus PCR test

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. AlcoTrue® M, [redacted]) will be performed at screening and prior to randomisation, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] with the exception of urine pregnancy tests. These tests will be performed at the trial site using Consult diagnostics® hCG Urine tests, or comparable test systems.

Laboratory data will be transmitted electronically from the laboratory to the trial site.

It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4).

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (i.e. Burdick ELI 150C) at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the trial.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

Local tolerability will be assessed by the investigator or qualified designee on the basis of swelling, induration, heat, redness, pain, and other findings. Tolerability will be assessed at Day 1 from the time of the injection until Day 2. Local findings assessed as clinically relevant by the investigator or qualified designee must be recorded as AE.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related or not.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities already pre-exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which, by their nature, can always be considered to be 'serious' even though they may not have met the criteria of an SAE as defined above.

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.
The following are considered as AESIs:

1. Potential severe DILI

   A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- o An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
- o Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided via the eDC. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

2. Anaphylactic reactions
3. Serious infection (defined as infections requiring IV antibiotics or meeting the regulatory definition of a SAE)
4. Hypersensitivity reactions

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced)

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- There is an alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned
- Disappearance of the event even though the trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.
- After the individual subject's end of trial:

- The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been sufficiently characterized (e.g. as 'chronic' or 'stable'), or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy, an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

Samples of whole blood (approximately 3 mL) will be taken (in tubes containing dipotassium ethylenediaminetetraacetic acid [K2EDTA] anticoagulant) at the time points shown in the Flow chart for the determination of concentrations of BI 695501.
Full instructions for collection, labelling, storage and shipment of samples are provided in the Laboratory Manual. After completion of the trial, selected PK samples may be retained and used for further methodological investigations, e.g., stability testing. The PK samples will be discarded after completion of the additional investigations, but not later than 5 years after the final Clinical Trial Report (CTR) has been signed.

Wherever possible, blood samples for other analyses will be taken at the same time as blood is drawn for PK analyses to limit repeated venipuncture.

In the event of early withdrawal from the trial, every effort should be made to take a PK sample as part of the early withdrawal procedures, if possible, with date and time of sample recorded.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.4.1 Drug-Drug Interaction Biomarkers

Not applicable.

5.4.2 Pharmacodynamic biomarkers

Not applicable

5.4.3 Pharmacogenomic biomarkers

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic and [redacted] parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of a subcutaneously administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration.

- The acceptable deviation from the scheduled time for vital signs, ECG, laboratory tests PK, [redacted] sampling) will be:
  - ±15 minutes for Day 1
  - ±2 hours from Day 2 to Day 10;
  - ±1 day from Day 15 to Day 57
  - The e.o.t. IGRA may be performed up to 72 hours prior to the other e.o.t. assessments.

If scheduled in the Flow Chart at the same time as a meal, blood sampling has to be done first.

For planned blood sampling times, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the trial.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

If possible, spare subjects will be provided for each group to guarantee the start of a complete group. The spare subjects will participate in all trial activities up to Day 1, i.e. on Day -1 they will be admitted to the clinic and all examinations, which have been scheduled up to drug administration on Day 1 will be performed. The spare subjects from one group will be given the option to participate in the next planned group.

6.2.2 Treatment period

On Day -1 trial participants will be admitted to the trial site and kept for 24 h following drug administration. The subjects will be allowed to leave the trial site on Day 2 after formal

assessment and confirmation of their fitness. On all other trial days, the trial assessments will be performed in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK, [redacted] and [redacted] analysis, refer to Flow Chart and in the Laboratory Manual.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining subject's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoT Visit.

If needed in the opinion of the investigator, additional visits may be scheduled after the EoT Visit for continued safety monitoring.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved.

Safety follow-up observational period will continue for 10 weeks after BI 695501 administration to collect AEs (SAEs).

The subjects are to be instructed to contact the investigator or his/her designee in case of occurrence of any AEs, any additional concomitant drug or if they undergo any medical treatment or any surgical procedure during the observational period until the safety follow-up (EoS) visit call. Subjects will be contacted by the investigator or designee 10 weeks after administration of the trial medication to collect the information on subject's wellbeing and document all AEs (SAEs) and concomitant medication.

All AEs, serious and non-serious, will be followed up until they have normalized or been sufficiently characterized and documented in the safety database.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of 40 mg BI 695501 100 mg/mL formulation (T) versus 40 mg BI 695501 50 mg/mL formulation (R) will be estimated by the ratios of the geometric means (T/R) for each primary endpoint, and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified and no significance level adjustment for multiple testing will be applied.

7.2 PLANNED ANALYSES

7.2.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The TS will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary and was without important protocol deviations or violations thought to significantly affect the PK of BI 695501 (as specified in 7.2.1.2). Descriptive and model based analyses of PK parameters will be based on the PKS.

Descriptions of additional analysis sets may be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be suggested in the iPD specification file. IPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

7.2.1.1 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 [redacted] for drug BI 695501 will be calculated according to the relevant procedures of the Sponsor.

Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol violation relevant for the evaluation. Reasons for exclusion of single pharmacokinetic parameters can for example be:

- Time deviations
- Use of restricted medications
- Dosing errors

Whether a protocol violation is important will be decided no later than in the Report Planning Meeting. It will also be decided in the Report Planning Meeting which subjects are to be excluded from the PKS. Subjects who are not included in the PKS (refer to Section 7.2.1) will be reported with their individual plasma concentrations and individual PK parameters;

however, they will not be included in descriptive statistics for plasma concentrations, PK parameters or other statistical assessments.

In case a pre-dose concentration value is greater than 5% of Cmax, the subject's PK data will not be included in any statistical evaluations, in accordance with international guidance. The individual PK parameters of such a subject will be calculated and listed separately. If a predose concentration is above the limit of quantification, but less than or equal to 5% of the subject's Cmax value, the subject's data without any adjustments will be included in all PK measurements and calculations.

Details of the analysis and presentation of PK data will be provided in the Trial Statistical Analysis Plan (TSAP).

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

7.2.2 Primary endpoint analyses

Primary analyses

The primary analysis is based on the PKS (see Section 7.2.1.1). The statistical model used for the analysis of the primary endpoints will be an analysis of covariance (ANCOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANCOVA model. This model will include effects accounting for the following sources of variation: 'treatment', 'location of trial medication injection' and 'baseline body weight'. The model is described by the following equation:

$y_{kjm} = \mu + \tau_k + \varphi_j + \beta \cdot weight_{km} + e_{kjm}$, where

y_{kjm} = logarithm of response on subject m receiving treatment k at location j,
μ = the overall mean,

τ_k = the k^{th} treatment effect, k = 1, 2,

φ_j = the j^{th} effect of location (thigh, abdomen), j= 1, 2,

β = the slope parameter for the baseline body weight covariable,

$weight_{km}$ = baseline body weight of subject m receiving treatment k

e_{kjm} = the random error associated with the m^{th} subject who received in location j treatment k

where $e_{kjm} \sim N(0, \sigma_k^2)$ are independent random variables.

Point estimates for the ratios of the geometric means (T/R) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means).

Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANCOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

In addition to the model based approach all parameters will be calculated and analysed descriptively.

7.2.3 Secondary endpoint analyses

Not applicable as no secondary endpoints specified.

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed at the Report Planning Meeting).

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All events with an onset after the first dose of trial medication up to a period of 10 weeks after the last dose of the trial medication (i.e., end of the REP) will be assigned to the treatment phase for evaluation, and will be referred to as treatment emergent adverse events (TEAEs). Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs and other significant AEs (according to ICH E3), and protocol-specified AESIs (see Section 5.2.6.1), will be listed separately.

The number and percentage of subjects with injection site reactions (assessed at Day 1 from the time of the injection until Day 2, prior to discharge from the trial site) will be summarized by treatment for each injection site reaction.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

Laboratory values taken after the first dose of trial medication up to a period of 10 weeks after the last dose of the trial medication will be assigned to the treatment phase for evaluation. Descriptive statistics of laboratory values over time and for the change from baseline will be provided for each treatment group. Laboratory parameters will be compared to their reference ranges and frequency tables will be provided for the number of subjects within and outside the reference range.

Observed values and changes from baseline in BP (systolic and diastolic), PR, and body temperature will be summarized by treatment group.

Details of the presentation and analysis of safety data will be provided in the TSAP.

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

With respect to AE analysis, missing relationship will be imputed to “yes”. For other safety evaluation, no imputation of missing data is planned.

7.3.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant procedures of the Sponsor.

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed)will not be considered for the non-compartmental analysis and the creation of graphs, except for concentration values in the lag phase identified as BLQ which will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

Descriptive statistics of parameters are calculated only when a parameter value is available for at least 2/3 of the treated individuals. If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead. PK parameters that cannot be determined will be identified as “not calculated”.

7.4 RANDOMISATION

Subjects will be randomized to one of the two treatments in a 1:1 ratio. The block size will be documented in the CTR. The randomization will be stratified by trial site for logistical reasons.

The sponsor will arrange for the randomization as well as packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.
The randomization list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of N=200 subjects in the trial including up to 10 subjects, that may be considered as non-PK evaluable (refer to Section 7.2), because this sample size is considered sufficient to assess the primary objective of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (T/R) can be expected with 95% probability. Precision is defined as the ratio of upper 90% confidence interval limit (CL) to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

In previous trials (1297.6 and 1297.13) the observed total geometric coefficient of variation (gCV) for the primary endpoints AUC and Cmax were in the range of 25% - 54%. The observed gCVs tended to be higher in trial 1297.6, in which the study drug was injected in lower abdomen only.

For various assumptions of the gCV, Table 7.5: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (T/R). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratio T/R of geometric means.

Table 7.5: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a parallel trial *(N=190)* assessing formulation differences

N	gCV [%]	Precision upper CL* / relative BA estimate	90% CI [%] of respective ratio**		
			100	105	110
190	25	1.066	(93.80; 106.61)	(98.49; 111.94)	(103.18; 117.27)
	40	1.105	(90.47, 110.54)	(94.99, 116.06)	(99.51, 121.59)
	50	1.131	(88.44, 113.07)	(92.86, 118.72)	(97.28, 124.38)

*CL = confidence interval limit
**Ratio of geometric means (T/R) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_P)$.

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230, Chapter 8] using R Version 4.02.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the CTR.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

eCRFs for individual subjects will be provided by the sponsor. See Section 4.1.5 for rules about emergency. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the subject, documented in their medical records, would be acceptable.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: gender, year of birth (in accordance with local laws and regulations)

- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including administration of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site:
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (e.g. biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first subject in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ('Last Subject Completed').

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI). The trial will be conducted in 2 sites - [redacted] and [redacted] A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required trial activities.
The trial will be managed by a FOT vendor based on a contract which specifies the delegated responsibilities and duties. BI has appointed a Clinical Trial Leader, responsible for coordinating all required activities, in order to:

- oversee and manage the trial in accordance with applicable regulations and SOPs,
- direct the clinical trial team and oversee the FOT vendor in the preparation, conduct, and reporting of the trial,
- ensure appropriate training.

In the participating country the trial will be performed by a Contract Research Organisation (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.
Data Management and Statistical Evaluation will be done by CRO according to BI and CRO SOPs.
Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI and CRO SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A local laboratories, and an analytical laboratory vendor will be used in this trial. Details will be provided in the Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group; 2010.

R17-4157 Cyltezo (adalimumab-adbm) injection, for subcutaneous use (U.S. prescribing information, revised: 8/2017). 2017.

R18-2637 Humira (adalimumab) injection, for subcutaneous use (AbbVie) (U.S.prescribing information, revised: 8/2018). 2018

R19-0075 Humira 20 mg solution for injection in pre-filled syringe, 40 mg/0.8 ml solution for injection, 40 mg solution for injection in pre-filled syringe, 40 mg solution for injection in pre-filled pen, 80 mg solution for injection in prefilled syringe, 80 mg solution for injection in pre-filled pen (AbbVie)(summary of product characteristics, last updated: 12/12/2018). 2018.

9.2 UNPUBLISHED REFERENCES

U13-1096-01 [redacted]. Pharmacokinetics and safety of BI 695501 in healthy subjects: a randomized, open-label, single-dose, parallel arm, active-comparator clinical Phase I study. 1297.1, 24 Jan 2013.

c03070713 [redacted]. Pharmacokinetics and safety of BI 695501 in healthy subjects: a randomized, open-label, single-dose, parallel arm, active-comparator clinical Phase I study. 1297.8. Version 2.0. 23 May 2016.

c08933656 Randomized, single-dose, parallel-arm, open-label Phase I trial to investigate and compare the pharmacokinetics, safety and tolerability of BI 695501 administered subcutaneously via prefilled syringe or autoinjector, (BI Trial 1297.6). Follow-up Clinical Trial Report. 28 Sep 2017.

c15874906 Randomized, single-dose, parallel-arm, open-label Phase I trial to investigate and compare the pharmacokinetics, safety and tolerability of BI 695501 administered subcutaneously to thigh via pre-filled syringe or autoinjector (BI Trial 1297.13). 30 May 2017.

c01835608 ib-bi-695501-1297-p1

10. APPENDICES

10.1 INSTRUCTIONS FOR USE

BI456906 or placebo Pre-Filled Syringe Instructions For Use

Important Safety Information

- DO NOT use the pre-filled syringe unless you have been trained to do so.
- DO NOT remove the protective cap until right before injection.
- DO NOT shake the pre-filled syringe.
- DO NOT use the pre-filled syringe if it is dropped or crushed.

Storage instructions

- Store the pre-filled syringe in a refrigerator between 36ºF to 46ºF (2ºC to 8ºC). Do not store the pre-filled syringe at the back of your refrigerator, where the pre-filed syringe's medication might freeze.
- Keep your pre-filled syringe in a dry and clean environment when warming up prior to use.
- Never subject your pre-filled syringe to extreme temperatures or direct sunlight (e.g., do not store your pre-filled syringe in a car or freezer).
- Keep the pre-filled syringe in the original carton until you are ready to use them.

Drug Administration:

Step 1

- Gather supplies (Pre-filled syringe, Alcohol wipe, Sharps Container) onto clean, flat surface in a quiet and well lift area.
- Take out of the fridge and wait 15–30 minutes for medication to warm to room temperature.
- Wash your hands with soap and water, then dry them completely.

Inspect the pre-filled syringe's medication, expiration date (on box), and body closely.

Step 2

Inspect pre-filled syringe closely:

Using the white tab at the top of the label unwrap the label carefully from around the syringe so you can see the medication.

It is normal to see one or more bubbles in the medication.

DO NOT use pre-filled syringe if:

- Pre-filled syringe has been left outside of the refrigerator or is stored at room-temperature 15- 25°C (59-77°F) for more than 2 hours.
- Medication is cloudy, is or was frozen, or contains flakes or particles.
- Pre-filled syringe appears cracked, damaged, or leaking.
- Pre-filled syringe has been used.
- Pre-filled syringe has been left in direct sunlight for an extended period of time.

Rewrap the label around the syringe.

Step 3

Select an injection site on the upper thighs or on the belly (at least 2ins/5cm away from navel).

- DO NOT inject an area near your waistline or navel.
- DO NOT inject into a tender, bruised or scarred area.
- DO NOT inject through clothes.

Step 4
Clean the injection site
Use an alcohol wipe to clean the injection site.
Let cleaned site air dry to avoid stinging.

- DO NOT fan or blow on clean site.
- DO NOT touch clean site before injecting.

Step 5
Remove needle cap
Gently pull cap straight off pre-filled syringe.
Dispose of the cap in general waste.

- DO NOT twist cap.
- DO NOT touch needle or let needle touch anything.
- DO NOT re-attach needle cap.

Step 6
Pinch and hold skin
Raise the skin of the injection site by loosely bringing your finger and thumb together on the sides of the injection site. Hold skin around cleaned injection site between finger and thumb. You will inject into this raised area of skin.
Step 10
Dispose of the device

- DO NOT re-attach needle cap.

Please dispose of the device in the sharps container.

10.2 MEDICATION BLINDING PROCEDURE FOR THIRD PARTY BLINDING

This is a double-blind trial, therefore subjects, Investigators, and trial personnel involved clinical conduct (except the trial personnel administering, receiving and handling the trial medication at site) will remain blinded with regard to the randomized treatment assignments until after database lock.

To prevent unblinding, a designated person will receive the trial medication and maintain records of the product's delivery to the trial site. In addition, a qualified unblinded designee will administer the trial medication, maintain the inventory at the site, as well as will be responsible for preparation of used trial medication for return to the sponsor or destruction in a blinded fashion and in accordance with local requirements.

Records of the product's delivery to the trial site will include dates, quantities, batch/serial numbers, expiry ('use by') dates and the unique code numbers assigned to the investigational products and trial patients. The designated unblinded person will maintain records that document doses administration to patients and reconcile all investigational product received at site. These records should be kept separate from the patients file and not be accessible for the blinded personnel. At the time of return to the sponsor or local destruction, the designated unblinded person must verify that no supplies remained at the trial site.

The unblinded trial personnel administering the trial medication will not be involved in any other trial assessments or procedures.

Patient blinding procedure
Trial medication will be administered by unblinded trial personnel on day 1.
To ensure patient's blinding during the administration process, the following procedures are to be applied:

- Syringes unpacked and prepared for injection are to be covered by a surgical drape at the time of patient preparation for dosing. The same procedure is to be applied to used syringes after injection.
- During the dose administration, patients are to be separated from the unblinded designee who will administer the trial medication, by surgical drape, screen or pillow.
- If a patient's dosing is required in a supine position, the screen or curtain (the way it is used during surgery) or towel are to be put at chest level.

Site staff blinding procedure
Responsibilities for blinded and unblinded study site staff are defined below. At the site, a form with the name(s) of the staff members, blinded and unblinded, with their respective responsibilities will be filled in.

(NOTE: all personnel noted below will have signed the Site Personnel Signature Log, clearly outlining each individual's responsibility).

In case of non-availability of blinded or unblinded study staff, the Clinical Research Organization and sponsor should be informed immediately.

Blinded Personnel	**Main Responsibilities**
Coordinating/principal Investigator: **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Monitors patient status • Responsible for the delegation of tasks to appropriate staff and to ensure correctness of all assessments • Provides direct patient care • Works and communicates with blinded CRA • Ensures adequate unblinded pharmacy staff and medication administrator and facilities
Blinded Sub-Investigator or Study Coordinator/Study Nurse: **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Monitors patient status • Provides direct patient care if applicable • Works and communicates with blinded monitor

Blinded CRA: **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS** **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Acts as the primary point of contact for the blinded site team • Provides ongoing site support in all areas of trial conduct, except accountability and reconciliation of trial medication • Conducts blinded site monitoring visits and performs source document verification

Unblinded Personnel	Main Responsibilities
Unblinded Pharmacist/Back-up Unblinded Pharmacist: **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS**	• Receives trial medication; unpacks, inventories and stores trial medication in a secure, limited access refrigerator • Responsible for the retention samples handling and documentation • Reviews temperature monitoring device for shipment temperature excursions • Acknowledges trial medication receipt • Completes the Master Drug Accountability Log and Subject Drug Dispensing Log • Monitors temperature using min/max. thermometer and completes refrigerator temperature storage log • Reports temperature excursions to unblinded monitor • Receives the kit numbers for injection from the sponsor • Dispenses trial medication to the unblinded medication administrator • Trains back-up pharmacist(s), if applicable • Implements blinding plan • Monitors and maintains drug inventory at site • Reports all protocol deviations regarding dosing errors to the unblinded CRA • Ensures all accountability logs are kept separate from the medication blinded staff • Works and communicates with unblinded monitor • Retains used kits for reconciliation by unblinded monitor prior to destruction. Destroys used medication per SOPs.
Set Unblinded Trial Medication Administrator: **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS**	• Cooperates with the unblinded pharmacist • Performs the trial medication administration and ensures patient is blinded during IP administration • Works and communicates with unblinded CRA
Unblinded CRA: **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS** **CANNOT ADMINISTER THE MEDICATION**	• Acts as the primary point of contact for the unblinded site team • Provides ongoing site support in the management of trial medication • Conducts unblinded site monitoring visits and monitors accountability of trial medication

CRA = clinical research associate

Training

All professional personnel taking part in the clinical trial are to be trained and aware of the need to respect study blinding principles as foreseen by the protocol. Blinded and unblinded study site staff as well as blinded and unblinded CRAs will be trained on study blinding procedures before the start of any study activities at site. Unblinded study site staff is restricted to persons handling trial medications including the injection of study drug. Training in study blinding procedures for blinded and unblinded study CRAs will be provided during a CRA Meeting. Training in study blinding procedures for blinded and unblinded site staff will be provided at the Investigators' Meeting; during workshop or WebEx sessions, separately designed for blinded and unblinded study personnel in which CRAs will participate, as well. Part of both workshops will review the Medication Blinding Procedures, with blinding procedures described. For the rest of site staff, who did not participate in an Investigators' Meeting, applicable training in study blinding procedures will be provided by a blinded CRA during the Site Initiation Visit, based on information in Study Protocol, Medication Blinding Procedures and Pharmacy Manual. Such training is a part of study specific agenda for Site Initiation Visit, as well as slide presentation prepared for the visit. All training will be documented.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE

Document Number: c36797272 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: Relative bioavailability of 40 mg/ 0.4 mL of BI 695501 compared to 40 mg/ 0.8 mL of BI 695501 formulation following single subcutaneous administrations in healthy male and female subjects (a double blind, randomized, single-dose, parallel-arm study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	26 Nov 2021 14:30 CET
Author-Trial Statistician		26 Nov 2021 14:30 CET
Approval-Team Member Medicine		26 Nov 2021 18:02 CET
Author-Clinical Pharmacokineticist		26 Nov 2021 19:48 CET
Approval-Therapeutic Area [redacted]		29 Nov 2021 17:56 CET
Verification-Paper Signature Completion		08 Dec 2021 10:43 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed